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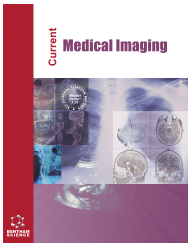

RESEARCH ARTICLE

Clinical, Radiological, and Microbiologic Characteristics of Patients with Non-cystic Fibrosis Bronchiectasis in a Tertiary Center at Jordan

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Abstract:

Background:

Only a small number of the investigations that were carried out in the Middle East attempted to characterize patients with NCFB. In order to characterize patients with NCFB, as well as their etiologies, microbiological profiles, and outcomes, we therefore carried out this investigation.

Methods:

This retrospective cohort study was carried out at the Jordan University Hospital (JUH), a tertiary facility located in Amman, Jordan. Non-cystic Fibrosis Bronchiectasis (NCFB) was defined as an HRCT scan typical for bronchiectasis along with a negative sweat chloride test to rule out cystic fibrosis. Patients' data were collected by the use of Electronic Medical Records (EMR) at our institution. Frequent exacerbation was defined as more than 2 exacerbations in 1 year of the onset of the diagnosis.

Results:

A total of 79 patients were included, and 54.4% of them were female. The mean and standard deviation of the patient's age was 48.61 ± 19.62. The etiologies of bronchiectasis were evident in 79.7% of the sample. Asthma, Chronic Obstructive Pulmonary Diseases (COPD), and Kartagener syndrome were the most prevalent etiologies, accounting for related illnesses in 21.8%, 21.5%, and 13.9% of the patients, respectively. The most frequent bacteria cultured in our cohort were Pseudomonas and Candida Species. Moreover, 43 patients of the study cohort were frequent exacerbators, and 5 patients died.

Conclusion:

Our study supports the need to identify several bronchiectasis phenotypes linked to various causes. These findings provide information to clinicians for the early detection and treatment of bronchiectasis in Jordan.

Keywords: Epidemiology, Bronchiectasis, Microbiology, Treatment, Patients, Non-Cystic fibrosis.

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1. INTRODUCTION

A prevalent illness and a significant contributor to respiratory morbidity is bronchiectasis [1]. It is defined as a persistent aberrant bronchial dilation accompanied by ongoing inflammation and infection [2]. Due to the failure of the airway defense mechanisms, the illness is characterized by a vicious cycle of prolonged bacterial infection and extreme neutrophilic inflammation [3]. Although it affects persons of all ages, it is more common in women and those over 60 [4]. The disease has a heavy social and economic toll due to increased morbidity, decreased quality of life, and long-term

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management costs [5]. The course of bronchiectasis' natural history varies. While some patients only get a few chest infections each year and do not experience a progressive disease over time, others experience more frequent and extended infectious episodes and develop respiratory failure more quickly, increasing the chance of death [3]. In the United Kingdom, from 2004 to 2013, the incidence of bronchiectasis in adults increased from 301 per 100,000 to 485 per 100,000 for men and from 350 per 100,000 to 566 per 100,000 for women. Likewise, in the United States, between 2000 and 2007, the annual prevalence of bronchiectasis in patients 65 years of age increased by 8.7% per year, and prevalence increased with age for both sexes but was greater for women [6, 7]. The available computed tomography (CT), which is required for diagnosis, is one of several confounding factors. The literature suggests that it changes depending on the geographic area [8, 9].

The underlying etiology of bronchiectasis is either unknown or related to a range of systemic illnesses in a large proportion of cases, leading to the term “idiopathic” [2]. It can be categorized into two types: cystic fibrosis and non-cystic fibrosis bronchiectasis [1]. The main etiologies of bronchiectasis are cystic fibrosis, alpha1-antitrypsin deficiency, primary ciliary dyskinesia, allergic bronchopulmonary aspergillosis, autoimmune/connective tissue diseases, inflammatory bowel diseases, congenital malformations, aspiration, humoral immunodeficiency, and post-infectious [3]. The most prevalent organisms that cause infections are Pseudomonas aeruginosa (12%–26%) and Haemophilus influenzae (47%-55%). However, they might also contain gram-negative pathogens, such as Staphylococcus aureus, Moraxella catarrhalis, Streptococcus pneumoniae, and others [8, 10, 11]. In up to 37% of individuals who come with bronchiectasis, determining the underlying etiology may change how they are managed [12].

Non-cystic fibrosis bronchiectasis (NCFB) is characterized by poor lung function caused by permanent and progressive damage of the airways [13]. Recurrent lung infections, sputum production, and cough are hallmarks of NCFB, which frequently necessitates hospitalization and long-term antibiotic therapy [14]. The ideal time to perform a high-resolution computed tomography scan of the chest is when the patient is clinically stable. This test is the gold standard for validating the diagnosis [15]. Typically, bronchiectasis has a cylindrical, varicose, or cystic appearance [3].

Treatment protocols are not yet clearly defined. Despite treatment, patients typically continue to experience symptoms and deterioration in respiratory function [1]. When a specific etiology is present, it is essential to identify it in order to adopt effective treatment for the underlying cause. All cases of bronchiectasis require treatment that targets infection, inflammation, and bronchial toilet regardless of whether a specific etiology can be determined [2]. Patient education, airway clearance, inhaled corticosteroids and β -agonists, antibiotic therapy, and long-term macrolide are the main methods of care. Surgery is typically only used for localized diseases that are resistant to medical treatment and are causing significant morbidity, including repeated or life-threatening hemoptysis [3].

In order to describe patients with NCFB [13], numerous research works were carried out all over the world, but only a small number of them were conducted in the Middle East and the Arabian region. We consequently decided to undertake this current study, which intended to characterize patients with NCFB along with their etiologies, microbiological profiles, and outcomes due to the dearth of data in our area.

2. METHODS

2.1. Design and Setting

This retrospective cohort analysis was carried out at the Jordan University Hospital (JUH), a tertiary facility in Amman. All patients admitted between 2010 and 2021 with non-cystic fibrosis bronchiectasis diagnosis proved by chest High-Resolution Computed Tomography (HRCT) scan were included. Patients with limited data about the definitive diagnosis, patients with a diagnosis of cystic fibrosis proved by sweat chloride, and patients without CT scan data that proved the diagnosis were excluded. The Institutional Review Board at JUH (10/2022/2493) gave its approval to this study. The IRB waived the need for written informed consent. The regulations and the guidelines of the Declaration of Helsinki were followed in conducting this study.

2.2. Data Collection

Non-cystic fibrosis bronchiectasis (NCFB) was the condition of interest. In order to rule out cystic fibrosis, NCFB was defined as an HRCT scan typical for bronchiectasis. Patients’ data were collected by the use of Electronic Medical Records (EMR) at our institution. The following variables were extracted: patients’ demographics, etiologies, number of exacerbations, sputum culture results obtained from the patients, spirometry results, patients’ outcomes, and radiologic findings of the HRCT and X-rays done at JUH. Frequent exacerbation was defined as more than 2 exacerbations within 1 year of the onset of diagnosis [16].

2.3. Data Analysis

Microsoft Office Excel 2019 was used to collect the participant data, which was imported into IBM SPSS v.25 software to perform the analysis. Continuous values were given as mean and standard deviation, whereas categorical variables were shown as counts and percentages.

3. RESULTS

3.1. The Characteristics of the Included Patients

There were 79 patients included in all. The mean and standard deviation of the patient's age was 48.61 ± 19.62, and 54.4% of them were female. The etiologies of bronchiectasis were evident in 79.7% of the sample. The most common etiologies were asthma, Chronic Obstructive Pulmonary Diseases (COPD), and Kartagener syndrome, as they were the associated conditions in 21.8%, 21.5%, and 13.9% of the patients, respectively. Other less common etiologies included previous tuberculosis infection, malignancy, and immunoglobulin deficiency. Furthermore, sputum culture was done in 83.5% of the patients. The culture results showed that Pseudomonas and Candida species were the most common

colonizing microorganisms, as they were found in 29.1% and 16.5% of the patients. In addition, Methicillin Resistant Staphylococcus Aureus (MRSA) was found in 5.1% of the patients. Results from chest X-rays revealed that multiple lobe involvement was the most typical pattern in the patients who were included. However, the left lower lobe and the right lower lobe were the lobes that were most frequently affected, each being implicated in 65.8% of the cases. Chest Computed Tomography (C.T) results showed that cylindrical pattern was the most common pattern found in the included patients (44.3%). The second most common pattern found in the included patients was the cystic pattern (34.2%), followed by the varicose pattern (17.7%). The Pulmonary Function Tests (PFT) of the study patients showed that the mean of Fractional Expiration Volume at 1 second was 54.41% ± 21.34%, and the mean of Forced Vital Capacity (FVC) was 57.3% ± 15.65%. Additionally, the mean of the FEV1/FVC ratio was 70.25% ± 13.08%. Regarding the outcomes of the patients, 54.4% had frequent exacerbations, and 6.3% of the study patients died (Table **1**).

Table 1. Baseline patient characteristics of the participants.

Variable	Response	Frequency (*n* = 79)	Percentage (%)
Sex	Male	36	45.6
	Female	43	54.4
Associated Conditions	COPD	9	11.4
	Asthma	17	21.8
	Kartagner Syndrome	11	13.9
	Immunoglobulins Deficiency	4	5.1
	Pulmonary Fibrosis	17	21.5
	Previous Tuberculosis	3	3.8
	Malignancy	2	2.5
	Unknown Cause	16	20.3
Sputum Culture	Pseudomonas Species	23	29.1
	Candida Species	13	16.5
	Klebsiella Species	6	7.6
	Acinetobacter Species	7	8.9
	Sphingomonas Species	3	3.8
	MRSA	4	5.1
	Streptococcus Species	2	2.5
	Penicillium Species	1	1.3
	E. coli	1	1.3
	Enterobacter Species	2	2.5
	Staphylococcus Species other than MRSA	1	1.3
	Not Done	16	20
X-ray Patterns	Right Upper Lobe	37	46.8
	Right Middle Lobe	44	55.7
	Right Lower Lobe	52	65.8
	Left Upper Lobe	42	53.2
	Left Lower Lobe	52	65.8
	Multiple Lobes	58	73.4
C.T Patterns	Cystic	27	34.2
	Cylindrical	35	44.3
	Varicose	14	17.7
	Traction	10	12.7
	Multiple Patterns	4	5.1
Outcome	Non-frequent Exacerbator	31	39.2
	Frequent Exacerbator	43	54.4
	Death	5	6.3
Variable	**Mean**	**SD**	**Range**
Age (years)	48.61	19.62	75
FEV1	54.41%	21.34%	106.00%
FVC	57.3%	15.65%	86.00%
FEV1/FVC	70.25%	13.08%	55.00%
Number of Exacerbations	2.39	1.96	9

3.2. The Characteristics of Bronchiectasis Frequent Exacerbators

Regarding the frequency of exacerbations, 43 patients were frequent exacerbators. Males made up 55.8% of the often exacerbating patients, and their average age was 46.70 ±17.78. Asthma and pulmonary fibrosis were the two conditions that these patients shared the most (25.6% and 18.6%, respectively). Whereas 11.6% of the frequent exacerbators had no identifiable etiology for their bronchiectasis. The most commonly colonizing microorganism in those patients was Pseudomonas and Klebsiella species, as they were isolated in 30.2% and 11.6% of the frequent exacerbators. On the other hand, MRSA was colonizing only 1 of those patients. Furthermore, a chest X-ray showed that the most common pattern among frequent exacerbators was multiple lobes involvement. The most commonly affected lobes were the right lower and left lower lobes, as these lobes were affected in 65.1% and 67.4% of those patients, respectively. Moreover, chest CT revealed that cylindrical pattern was the most common in those patients (41.9%), followed by cystic pattern (30.2%). The PFT showed that the mean of FEV1 and FVC were 50.91% ± 23.47% and 56.02% ± 16.85%, respectively. The mean number of exacerbations in those patients was 3.37 ± 2.11 (Table **2**).

Table 2. The characteristics of frequent exacerbators in bronchiectasis patients.

Variable	Response	Frequency (*n* = 43)	Percentage (%)
Sex	Male	24	55.8
	Female	19	44.2
Associated Conditions	COPD	4	9.3
	Asthma	11	25.6
	Kartagner Syndrome	7	16.3
	Immunoglobulins Deficiency	3	7.0
	Pulmonary Fibrosis	8	18.6
	Previous Tuberculosis	3	7.0
	Malignancy	2	4.7
	Unknown Cause	5	11.6
Sputum Culture	Pseudomonas Species	13	30.2
	Candida Species	4	9.3
	Klebsiella Species	5	11.6
	Acinetobacter Species	4	9.3
	Sphingomonas Species	3	7.0
	MRSA	1	2.3
	Streptococcus Species	2	4.7
	Penicillium Species	0	0
	E. coli	0	0
	Enterobacter Species	1	2.3
	Staphylococcus Species other than MRSA	1	2.3
X-ray Patterns	Right Upper Lobe	21	48.8
	Right Middle Lobe	25	58.1
	Right Lower Lobe	28	65.1
	Left Upper Lobe	24	55.8
	Left Lower Lobe	29	67.4
	Multiple Lobes	33	76.7
C.T Patterns	Cystic	13	30.2
	Cylindrical	18	41.9
	Varicose	10	23.3
	Traction	6	14.0
	Multiple Patterns	3	7.0
Variable	**Mean**	**SD**	**Range**
Age (years)	46.70	17.78	65
FEV1	50.91%	23.47%	86.00
FVC	56.02%	16.85%	86.00%
FEV1/FVC	67.00%	14.69%	55.00%
Number of Exacerbations	3.37	2.11	9

Table 3. The characteristics of the dead patients with bronchiectasis.

Variable	Response	Frequency (*n* = 5)	Percentage (%)
Sex	Male	1	20.0
	Female	4	80.0
Associated Conditions	COPD	1	20.0
	Asthma	0	0
	Kartagner Syndrome	2	40.0
	Immunoglobulins Deficiency	0	0
	Pulmonary Fibrosis	2	40.0
	Previous Tuberculosis	0	0
	Malignancy	0	0
	Unknown Cause	0	0
Sputum Culture	Pseudomonas Species	1	20.0
	Candida Species	2	40.0
	Acinetobacter Species	2	40.0
X-ray Patterns	Right Upper Lobe	3	60.0
	Right Middle Lobe	2	40.0
	Right Lower Lobe	3	60.0
	Left Upper Lobe	2	40.0
	Left Lower Lobe	4	80.0
	Multiple Lobes	3	60.0
C.T Patterns	Cystic	1	20.0
	Cylindrical	4	80.0
	Varicose	0	0
	Traction	0	0
	Multiple Patterns	0	0
Variable	**Mean**	**SD**	**Range**
Age (years)	43.60	20.06	53
FEV1	58.00%	29.15%	81.00%
FVC	57.80%	16.12%	15.12%
FEV1/FVC	73.00%	15.12%	41.00
Number of Exacerbations	2.60	1.82	4

3.3. The Characteristics of the Dead Patients with Bronchiectasis

In terms of the patients' results, 5 patients died. The majority of patients who passed away were female patients (80%), and their average age was 43.60± 20.06. Kartagener syndrome and pulmonary fibrosis were the causes of death in 40.0% of bronchiectasis patients, making them the most prevalent etiologies. The sputum culture results showed that Candida (40.0%), Acinetobacter (40.0%), and Pseudomonas species were the microorganisms that were colonizing those patients. Chest X-rays of those patients showed that the left lower lobe (80.0%) and the right lower lobe (60.0%) were the most commonly involved lobes, whereas multiple lobes were involved in 60.0% of the patients. Moreover, the chest CT results showed that cylindrical (80.0%) and cystic patterns (20.0%) were the only patterns observed in those patients. Regarding the PFT results, the mean of FEV1 of those patients was 58.00% ± 29.15%, while the mean FVC was 57.80% ± 16.12%. Also, the mean FEV1/FVC ratio of the patients was 73.00% ± 15.12%. In addition, the mean number of exacerbations was 2.60 ± 1.82 (Table **3**).

4. DISCUSSION

Our analysis showed that 54.4% of our patients were females, and the mean age was 48.61 ± 19.62. Similar to our study, a study in Spain demonstrated that 55% of their patients were females, yet their mean age was 64.9 [17]. The higher mean age in this study was due to the older population in Europe compared to the population in Asia. A study conducted in Taiwan demonstrated that the mean age was around 50, which is quite similar to our findings [17]. It is significant to note that studies have found that older persons had higher symptom rates and lower quality of life [18]. In this population, multimorbidity was linked to an increased risk of hospitalization, life-threatening exacerbations, and mortality [18]. Regarding the etiologies of the disease, the most common etiology was asthma, followed by COPD and Kartagener syndrome. Another study in Taiwan demonstrated similar findings as it showed that COPD and asthma were common causes of bronchiectasis, and each accounted for around 15% of the etiologies in their cohort [17]. Studies showed that COPD and asthma-induced bronchiectasis were associated with poorer lung function and higher mortality [19, 20]. It was shown that chronic bronchial infection was associated with higher bacterial load bronchiectasis in patients with COPD,

leading to high local and systemic inflammation and greater frequency and severity of exacerbations despite the fact that a causal relationship between bronchiectasis and COPD remains to be determined [21 - 23]. As a result, it may be reasonable to speculate that COPD, especially when it is accompanied by recurring infections and exacerbations, maybe a root cause of bronchiectasis without any other known etiology. The literature showed that post-infectious bronchiectasis is a common etiology and accounts for 20%-70% of the cases [17, 24, 25]. Post-infectious bronchiectasis was mainly driven by tuberculosis in the studies. In our study only minority of the cases were due to tuberculosis; however, studies in Taiwan [17], China [25], and Australia [26] showed that post-tuberculosis bronchiectasis was the most common cause in their cohort studies. This discrepancy can be explained by the low incidence of tuberculosis cases in Jordan compared to other countries, especially in Asia. Also, idiopathic bronchiectasis accounted to be around 20% of our cases, which is compatible with what other literature and studies reported, ranging between 6% and 77% [17, 24, 25]. The literature involving bronchiectasis was reported to be highly variable due to the differences in enrolled patients and whether the diagnosis was based on diagnostic exams or databases. Our study was based on medical records; hence, it might be less variable compared to other studies that might have depended on less reliable sources for patients' data. It is worth mentioning that the microbiologic characteristics are different between studies due to the different geographic distribution. The most common bacteria in our cohort were *P.* aeuroginosa and Candida Albicans. Studies in other literature also showed that the most common organism was *P.* aeuroginosa [17, 24]; however, Non-Tuberculous Mycobacteria was also common, especially in patients with post-infectious bronchiectasis [17]. Furthermore, it was demonstrated that the microbiology spectrum is different according to the etiology [27]. According to a study conducted in India, P. aeruginosa, Enterobacteriaceae species, and S. aureus were the most common pathogens in the post-infection and idiopathic groups, while NTM was uncommon in the cohort [27]. Additionally, PFT in our cohort showed low FEV1 and FEV1/FVC means, which is consistent with the most common etiologies of bronchiectasis, *i.e.*, COPD and asthma.

We found that the majority of the frequent exacerbators were males with asthma or pulmonary fibrosis. In the majority of them, Pseudomonas and Klebsiella were the most commonly isolated organisms. Previous studies showed that obstructive lung diseases and Pseudomonas species infections were risk factors for frequent exacerbations [16]. Additionally, the majority of the patients had multi-lobar disease, which is consistent with the findings in a study conducted in Ukraine [28]. Regarding mortality, the majority of the patients who died were females, and the etiology of their disease was Kartagener syndrome or pulmonary fibrosis. The majority of them had Candida species and Acinetobacter. Studies demonstrated that the most common cause of death among bronchiectasis patients was respiratory causes and lung cancer [29]. Studies also showed that patients with comorbidities, including diabetes, asthma, COPD, malignancy, cardiac diseases, and inflammatory bowel disease, had a higher mortality rate among others [30]. In addition, studies showed that an increase in the number of comorbidities was also a risk for mortality [31].

LIMITATIONS

Given that this is the first study on bronchiectasis to be undertaken in Jordan and one of the few in the Middle East, there are a number of limitations that must be addressed. First, our study is a single cohort study, which limits the generalizability of our results. Second, the low sample size also limited the generalizability and our ability to investigate the risk factors of frequent exacerbations and mortality. Additionally, we did not include several laboratory data, such as antibiotic resistance and immunoglobulin levels. Finally, JUH is a tertiary referral hospital; therefore, the data we introduced in our study might not be representative of the general population of bronchiectasis patients and might be skewed to patients with a more severe and progressive course of this disease.

CONCLUSION

We presented the data of 79 patients with bronchiectasis. The most common etiologies of bronchiectasis were asthma and COPD. The most frequent bacteria cultured in our cohort were Pseudomonas and Candida Species. The majority of frequent exacerbators were males and had asthma and *P.* aeruginosa. In addition, the majority of patients who died were females and had Kartagener syndrome and candida species. Different bronchiectasis phenotypes associated with different causes should be identified. These findings offer data for clinicians for early diagnosis and management of bronchiectasis in Jordan.

AUTHOR'S CONTRIBUTION

This study's conceptualization was provided by ASA and TA. Data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, and writing the first draft were all performed by AAT, ASA, TA, MM, DMA, SFA, AA, and RHA. ASA and AAT were also responsible for supervising, reviewing, and editing the manuscript, and ESB was responsible for editing the manuscript.

LIST OF ABBREVIATIONS

JUH	=	Jordan University Hospital
NCFB	=	Non-cystic fibrosis bronchiectasis
EMR	=	Electronic Medical Records
HRCT	=	High-Resolution Computed Tomography
COPD	=	Chronic Obstructive Pulmonary Disease
MRSA	=	Methicillin-resistant Staphylococcus Aureus
PFT	=	Pulmonary Function Tests

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethical Institutional Committee of the Institutional Review Board at JUH (10/2022/2493).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

The IRB waived the need for written informed consent.

STANDARD OF REPORTING

STROBE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

On reasonable request, the corresponding author can provide data associated with this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] King P, Holdsworth S, Freezer N, Holmes P. Bronchiectasis. Int Med J 2006; 36: 729-37. [http://dx.doi.org/10.1111/j.1445-5994.2006.01219.x]

[2] Lazarus A, Myers J, Fuhrer G. Bronchiectasis in adults: A review. Postgrad Med 2008; 120(3): 113-21. [http://dx.doi.org/10.3810/pgm.2008.09.1912] [PMID: 18824830]

[3] King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med 2006; 100(12): 2183-9. [http://dx.doi.org/10.1016/j.rmed.2006.03.012] [PMID: 16650970]

[4] Q JK. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: A population-based cohort study. Eur Respir J 2016; 47(1): 186-93. [http://dx.doi.org/10.1183/13993003.01033-2015]

[5] McDonnell MJ, Ward C, Lordan JL, Rutherford RM. Non-cystic fibrosis bronchiectasis. QJM 2013; 106(8): 709-15. [http://dx.doi.org/10.1093/qjmed/hct109] [PMID: 23728208]

[6] Goeminne P, Dupont L. Non-cystic fibrosis bronchiectasis: Diagnosis and management in 21st century. Postgrad Med J 2010; 86(1018): 493-501. [http://dx.doi.org/10.1136/pgmj.2009.091041] [PMID: 20709772]

[7] Stafler P, Carr SB. Non-cystic fi brosis bronchiectasis: Its diagnosis and management. Arch Dis Child Educ Pr 2010; 5: 73-82. [http://dx.doi.org/10.1136/adc.2007.130054]

[8] Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. Chest 2012; 142(2): 432-9. [http://dx.doi.org/10.1378/chest.11-2209] [PMID: 22302301]

[9] Hess EP, Haas LR, Shah ND, Stroebel RJ, Denham CR, Swensen SJ. Trends in computed tomography utilization rates: A longitudinal practice-based study. J Patient Saf 2014; 10(1): 52-8. [http://dx.doi.org/10.1097/PTS.0b013e3182948b1a] [PMID: 24080717]

[10] Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: A comprehensive profile of a neglected disease. Eur J Intern Med 2003; 14(8): 488-92. [http://dx.doi.org/10.1016/j.ejim.2003.10.002] [PMID: 14962701]

[11] Wilson C B, Jones P W, Leary C J O, Cole P J, Wilson R. Validation of the St. George's respiratory questionnaire in bronchiectasis. Am J Respir Crit Care Med 1997; 156(2): 536-41. [http://dx.doi.org/10.1164/ajrccm.156.2.9607083]

[12] Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. Respir Med 2007; 101(6): 1163-70. [http://dx.doi.org/10.1016/j.rmed.2006.11.008] [PMID: 17223027]

[13] Imam JS, Duarte AG. Non-CF bronchiectasis: Orphan disease no longer Respir Med 2020; 166: 105940. [http://dx.doi.org/10.1016/j.rmed.2020.105940]

[14] Paredes Aller S, Quittner AL, Salathe MA, Schmid A. Assessing effects of inhaled antibiotics in adults with non-cystic fibrosis bronchiectasis—experiences from recent clinical trials. Expert Rev Respir Med 2018; 12(9): 769-82. [http://dx.doi.org/10.1080/17476348.2018.1503540] [PMID: 30025482]

[15] King MA, Neal DE, St John R, Tsai J, Diaz PT. Bronchial dilatation in patients with HIV infection: CT assessment and correlation with pulmonary function tests and findings at bronchoalveolar lavage. AJR Am J Roentgenol 1997; 168(6): 1535-40. [http://dx.doi.org/10.2214/ajr.168.6.9168720] [PMID: 9168720]

[16] Chalmers JD, Aliberti S, Filonenko A, *et al.* Characterization of the "Frequent Exacerbator Phenotype" in Bronchiectasis. Am J Respir Crit Care Med 2018; 197(11): 1410-20. [http://dx.doi.org/10.1164/rccm.201711-2202OC] [PMID: 29357265]

[17] Olveira C, Padilla A, Martínez-García MÁ, *et al.* Etiology of bronchiectasis in a cohort of 2047 patients. An analysis of the spanish historical bronchiectasis registry. Arch Bronconeumol 2017; 53(7): 366-74. [http://dx.doi.org/10.1016/j.arbr.2017.05.005] [PMID: 28118936]

[18] Tc F, Wilson R, Skrbic D, *et al.* Comorbidities and the risk of mortality in patients with bronchiectasis: An international multicentre cohort study Lancet Respir Med 2016; 4(12): 969-79. [http://dx.doi.org/10.1016/S2213-2600(16)30320-4] [PMID: 27864036]

[19] Ip MS, So SY, Lam WK, Yam L, Liong E. High prevalence of asthma in patients with bronchiectasis in Hong Kong. Eur Respir J 1992; 5(4): 418-23. [http://dx.doi.org/10.1183/09031936.93.05040418] [PMID: 1563501]

[20] Martínez-García MÁ, Soler-Cataluña JJ, Donat Sanz Y, *et al.* Factors associated with bronchiectasis in patients with COPD. Chest 2011; 140(5): 1130-7. [http://dx.doi.org/10.1378/chest.10-1758] [PMID: 21546440]

[21] Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: A systematic review and meta-analysis. PLoS One 2016; 11(3): e0150532. [http://dx.doi.org/10.1371/journal.pone.0150532] [PMID: 26978269]

[22] Patel IS, Vlahos I, Wilkinson TMA, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170(4): 400-7. [http://dx.doi.org/10.1164/rccm.200305-648OC] [PMID: 15130905]

[23] Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, *et al.* Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013; 187(8): 823-31. [http://dx.doi.org/10.1164/rccm.201208-1518OC] [PMID: 23392438]

[24] Chandrasekaran R, Mac Aogáin M, Chalmers JD, Elborn SJ, Chotirmall SH. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. BMC Pulm Med 2018; 18(1): 83. [http://dx.doi.org/10.1186/s12890-018-0638-0] [PMID: 29788932]

[25] Palwatwichai A, Chaoprasong C, Vattanathum A, Wongsa A, Jatakanon A. Clinical, laboratory findings and microbiologic characterization of bronchiectasis in Thai patients. Respirology 2002; 7(1): 63-6. [http://dx.doi.org/10.1046/j.1440-1843.2002.00367.x] [PMID: 11896903]

[26] Steinfort DP, Brady S, Weisinger HS, Einsiedel L. Bronchiectasis in central australia: A young face to an old disease. Respir Med 2008; 102(4): 574-8. [http://dx.doi.org/10.1016/j.rmed.2007.11.007] [PMID: 18086522]

[27] Dhar R, Singh S, Talwar D, *et al.* Bronchiectasis in India: Results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and respiratory research network of india registry. Lancet Glob Health 2019; 7(9): e1269-79. [http://dx.doi.org/10.1016/S2214-109X(19)30327-4] [PMID:

31402007]
[28] Gashynova K, Suska K, Dmytrychenko V. Factors affecting the frequency of exacerbations in adult patients with bronchiectasis. Wiad Lek 2020; 73(8): 1717-22.
[http://dx.doi.org/10.36740/WLek202008124] [PMID: 33055340]
[29] Sin S, Yun SY, Kim JM, *et al.* Mortality risk and causes of death in patients with non-cystic fibrosis bronchiectasis. Respir Res 2019; 20(1): 271.
[http://dx.doi.org/10.1186/s12931-019-1243-3] [PMID: 31796019]
[30] Clofent D, Álvarez A, Traversi L, Culebras M, Loor K, Polverino E. Comorbidities and mortality risk factors for patients with bronchiectasis. Expert Rev Respir Med 2021; 15(5): 623-34.
[http://dx.doi.org/10.1080/17476348.2021.1886084] [PMID: 33583300]
[31] Adam N, Katarzyna S, Maria S, Michal B, Robert P, Pawel S. The influence of comorbidities on mortality in bronchiectasis: A prospective, observational study. Adv Clin Exp Med 2021; 30(12): 1315-21.
[http://dx.doi.org/10.17219/acem/144200] [PMID: 34918883]